The use of methods based on the theory of dynamical systems for mathematical modeling in biomedical research

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Abstract  More recently there has been a considerable interest in the development of new methods for the mathematical modeling of processes in biomedicine. Consequently, several new modeling methods have gradually emerged in a series of articles such as Computer Methods and Programs in Biomedicine, Journal of Pharmacokinetics and Pharmacodynamics, Journal of Pharmaceutical Sciences, European Journal of Pharmaceutical Sciences, Drug Metabolism and Disposition, etc. Simultaneously, the development of mathematical models of various dynamical processes in biomedicine has become one of the most rapidly growing and exciting application-oriented sub-disciplines of the mathematical modeling. The goals of this study are twofold. Firstly, to briefly describe a modeling method not widely used in biomedical research. Secondly, to arouse the interest of the audience in the method described, for example researchers in biomedical research and students in scientific or biomedical training programs.

INTRODUCTION

The aim and purpose of this study is, firstly, to briefly describe a modeling method which is not widely used by researchers in conducting studies of the pharmacokinetic behavior of drugs, i.e. a method based on the theory of dynamical systems, see for example, studies [1] [2] [3] [4] [5] [6] [7] [8] [9] [10] [11], and secondly, to arouse the interest of the audience in the method described, for example: biomedical researchers and/or students in scientific research. The modeling method described here is likely to be useful for helping practicing scientists in biomedicine to consider problems solved from different perspectives and to identify the relevant issues arising from those perspectives.

The theory of dynamical systems provides a coherent and unified framework for developing mathematical models of complex biomedical systems and investigating various phenomena in biomedicine with the aid of dynamical systems.

Methods based on the theory of dynamical systems are commonly used in system engineering practice [1]. These methods can be used also in biomedicine to develop models of diverse dynamical processes occurring in biomedical systems. For example: processes associated with pharmacokinetic behavior of drugs [2] [3] [4], metabolite formation [5] drug dissolution [6] [7] drug effect [8] and processes related to physiology [9].

In order to exemplify the use and applicability of tools from the theory of dynamical systems in biomedicine a theoretical pharmacokinetic example is used in the current study, because pharmacokinetics can be considered as a particular part of biomedicine.
pharmacokinetic example and the illustration in Figure 1 are used. Throughout, care is taken to define a minimal set of assumptions. The assumptions are as follows: 1) a drug is administered intravenously to a hypothetical subject, 2) a drug is administered either in a single bolus dose, or in a short time infusion, or by multiple bolus doses, 3) the site of measurement of the plasma concentration time profiles of the drug administered is the same after a single bolus dose of the drug, after and during short time infusion of the drug, and also during after multiple bolus doses of the drug, 4) physiological properties of the body do not change during the experiment. The schematically illustrated the drug administration is shown in Figure 1 in the column headed “INPUTS”. The schematically illustrated the resulting plasma concentration-time profiles of the drug can be found in the column headed “OUTPUTS”. If traditional pharmacokinetic methods are used to analyze the data, significantly different models of the pharmacokinetic behavior of the drug administered are obtained. The reason for this is as follows: Traditional pharmacokinetic modeling methods are based on modeling plasma concentration-time profiles of drugs administered. Since plasma concentration-time profiles of the drugs administered are different, different models of the pharmacokinetic behavior of drugs administered are obtained, see for example, the illustration in Figure 1. On the contrary, if a method based on the theory of dynamical systems is used, essentially the same models would be obtained for the pharmacokinetic behavior of the drug after single bolus dose of the drug, short time infusion of the drug, and multiple dosing of the drug, assumed in the current study. The reason for this is that the latter model depends only on physiological properties of the body and the ADME properties of the drug administered. Therefore, for example, the latter model is the same after the three different modes of drug administration assumed in the theoretical pharmacokinetic example in the current study. ADME is a well-known acronym in pharmacokinetics for absorption, distribution, metabolism, and excretion [12].

Over the years, analogous models of the pharmacokinetic behavior of drugs have been developed see, for example, studies [2] [3] [4] [5] [6] [7] [8] [9] [10] [11]. In general, models of pharmacokinetic behavior of drugs developed using tools from the theory of dynamical systems can be described by their ability to be used in more than one case of application. Such an example was presented in the study [10] where such a model of the pharmacokinetic behavior of factor VIII in hemophilia A patients was used to adjust factor VIII dosing aimed at achieving and then maintaining required plasma concentration-time profiles of factor VIII in hemophilia A patients.
The creation of a dynamical system representing the pharmacokinetic behavior of a drug is a simple procedure. It can be performed in the following way: a function approximating a drug input into the body is used as an input into a dynamical system, and a function approximating a response of the body to the drug input is used as an output of a dynamical system, see, for example, the studies [3] [4] [5] [6] [7] [8] [9] [10] [11].

Modeling dynamical systems

The computer program named CTDB was developed to model dynamical systems (2). A demo version of CTDB is available at: http://www.uef.sav.sk/durisova.htm. The computer program CTDB uses a transfer function model, see for example studies [3] [4] [5] [6] [7] [8] [9] [10] [11].

The transfer function model used is defined in the complex domain. Therefore, for modeling purposes the transfer function model is transformed into an equivalent model in the frequency domain, see for example, the studies [13] [14].

Using the computer program CTDB, point estimates of the parameters of the frequency model are obtained using the Levy method [15]. An optimal structure of the frequency model is found by minimizing the Akaike information criterion [16].

A practical use of a transfer function model and a frequency model in pharmacokinetics having been presented in several articles authored or co-authored of the author of the current study; see the full text articles at http://www.uef.sav.sk/advanced.htm. For example, the transfer function model was used in the study [17] to derive a very simple general and mathematically elegant formula for the calculation mean residence time of a drug administered.

Discussion

The models considered here are not commonly used in biomedicine. The reason for this is probably the lack of experience working with computer programs employing the models considered here and lack of adequate mathematical knowledge.

In the time domain, the development of a mathematical model of a dynamical system is a time consuming and complicated task, due to lack of a priori information on an appropriate model structure. The model development can be facilitated by a combination of modeling methods from the frequency and time domain, see, for example, the studies [2] [3] [4] [5] [6] [7] [8] [9] [10] [11]. A combined modeling method implemented in the computer program CTDB exhibits specific advantages: 1) it does not require a priori knowledge about the dynamical system under study; 2) it allows a rapid identification of an appropriate model structure; 3) it starts with a fast non-iterative algorithm that speeds up modeling process [13]; 4) it allows to develop mathematical models of diverse dynamical processes occurring in biomedical systems in a unified way.

In the current study: 1) the dynamical system is used as a working tool; 2) biomedicine is understood as the branch of medical science that deals with applications of the principles of the natural sciences, especially biology and physiology, to medicine; 3) the dynamical system used is an abstract mathematical construct, without any biological relevance; 4) the terminology commonly used in system engineering practice is employed. The terminology employed is significantly different from the terminology commonly used in biomedical practice. It can be asserted with certainty that there is an essential difference between the physiological nature of the information conveyed by a physiological system and the functional nature of the information conveyed by the dynamical system used in the current study. A physiological system is any system that contributes to the functioning of the human body. It may include any of the organs, for example: cardiovascular system (blood vessels and heart) nervous system (brain, spinal cord and nerves) respiratory system (lungs, associated blood supply and bronchial tree) renal system (kidney filtration) endocrine system (hormone production, release and action). In the current study, the dynamical system is used as means to mathematically represent the dynamical process under study. Another difference is related to the use of the term „dynamic”: In biomedicine, (and especially in pharmacokinetics) the term „dynamic” is widely used in descriptions of drug actions. In the current study the term “dynamical” is used to indicate continuous changes in the process under study. The differences in terminology outlined above do not have any consequence on pharmacokinetics. The dynamical system presented in the current study does not attempt to encompass all the processes that influence pharmacokinetic behavior of the drug administered. Therefore the dynamical system presented is an abstraction of reality.
Concurrently, the author would like to stress that by the current study does not want in any way to denigrate the importance of other methods for development of mathematical models which are used in biomedicine. In addition the author would like to stress that mathematical details of the outlined method are not given, therefore the author hopes, that the material presented will be accessible also to “non-mathematically-oriented” readers.

Modeling methods based on the theory of dynamical systems can be used to develop mathematical models of the pharmacokinetic behavior of a drug without any prior knowledge or hypothesis concerning the pharmacokinetic behavior of a drug. This is a great advantage of the modeling methods based on the theory of dynamical systems when compared, for example, with compartmental modeling methods.

From the author’s long-term experience, it can be concluded that the modeling methods based on the theory of dynamical systems represent a promising alternative for diverse modeling methods traditionally used in biomedicine and especially in pharmacokinetics.

Declarations
This study is dedicated to the memory of Professor Luc Balant who passed away on December 20, 2013. Internationally, Professor Luc Balant was best known for his for his significant contributions to pharmacokinetics, work in the COST Domain Committee for Biomedicine and Molecular Biosciences and work in the COST Action B15: “Modeling During Drug Development”.

The motto of this study could have been: “The undergoing physical laws necessary for the mathematical theory of a large part of physics and of the whole chemistry are thus completely known, and difficulty is only that the exact application of these laws leads to equations much more complicated to be soluble”. An outstanding theoretical physicist P. A. M. Dirac (1902-1984).

About the Author
Mária Ďurišová is a principal research scientist with the Department of Pharmacology of Inflammation of the Institute of Experimental Pharmacology and Toxicology, Slovak Academy of Sciences Bratislava, Slovak Republic, where she works in the area of mathematical modeling various dynamical systems. For more information about the modeling methods used by Mária Ďurišová and their application in pharmacokinetic studies please visit: www.uef.sav.sk/durisova.htm

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Conflict of interest
The author has reported no potential conflicts of interest relevant to this article.

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